

Appendix 6

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Joseph G. Valentino, Esq.
Senior Vice President, Secretary, and General Counsel
United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
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Re.: USAN Review Board / Winston Laboratories

Dear Mr. Valentino:

This letter is in response to Winston Laboratories' statement dated June 20, 2003, in which they dispute the USAN Council's (Council) basis for opposition to their appeal to change the established USAN and INN, zucapsaicin, for *cis*-8-methyl-*N*-vanillyl-6-nonenamide. The Council's responses to each of Winston Laboratories' (Winston's) allegations (indicated by **bold face** or *italics*) are set forth below.

"Zucapsaicin" violates several key USAN Guiding Principles for Nonproprietary Drug Names (Guiding Principles).

1. *"The name "zucapsaicin" violates General Rule # 4: "A name should be free from conflict with other nonproprietary names and with established trademarks; it should be neither confusing nor chemically misleading.""*

USAN Response

The name zucapsaicin clearly identifies this compound as an isomer of capsaicin. The only difference between zucapsaicin and capsaicin is the question of stereochemistry, as noted by the stereochemical indicators *Z* (*cis*) vs *E* (*trans*). Anecdotal evidence aside, any health care practitioner can clearly understand that capsaicin and zucapsaicin are related. The USAN Council's first general rule is that "...A nonproprietary name should be useful primarily to health practitioners, especially physicians, pharmacists, nurses, educators...." The name civamide only indicates that this compound is chemically an amide.

One must also review the history of the negotiation with Winston and their predecessor, GenDerm, to note that the only reason the prefix "zu" was used instead of the prefix "cis" was that GenDerm objected to the prefix "cis", and indicated in their letter dated July 13, 1993, that they prefer "zu" to "cis" in the nonproprietary designation for their product. The name zucapsaicin was the result of prolonged negotiation between GenDerm, the USAN Council, and the INN Committee.

Winston also points out that the syllable "zu" is used to identify humanized monoclonal antibodies. The nomenclature scheme for monoclonal antibodies was not developed until the mid-1990's. As noted in our previous letter, there is no chance of confusion, as "zu" is used only as an infix in monoclonal antibodies, which are biological substances that by nature are complicated substances, hence the complicated nomenclature scheme. This scheme was developed by the Center for Biologics and Research (CBER) of the Food and Drug Administration (FDA), along with international experts in biologics from the World Health Organization (WHO), as well as the International Nonproprietary Name (INN) Committee and the USAN Council.

Granted, the two examples, zuclophene and zuclopenthixol, are older substances, however the prefix "zu" is used correctly. One must note that when coining a new name for a substance, not only are USAN taken into consideration, but INN as well. Thus it may appear that zuclophene was coined first; however clomiphene was coined first, and zuclophene and enclomiphene were coined thereafter.

The USAN Council concurs that much has changed since the 1960's, and the development of new stems and new nomenclature schemes by the USAN Council since the early years certainly documents the changes. However, this does not mean that decisions made earlier are erroneous. The Council is certainly aware of medication errors caused by look-alike/sound-alike drug names, and is actively involved in reviewing such errors through the USP's Medication Errors Program and the Institute for Safe Medication Practices, as well as with our FDA liaison through FDA's Office of Drug Safety.

2. *The name "zucapsaicin" violates General Rule #5: "Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks."*

USAN Response

The USAN Council deliberated on the name civamide on more than one occasion, and the name was found to be in conflict with existing names and did not conform to the guiding principles. Although there were only two articles in existence in December 1992, both Winston and its predecessor GenDerm continued to use the name civamide in the literature and in their documentation.

By law, zucapsaicin is the FDA-recognized, established nonproprietary name, and has been since 1994. Winston continued to use the name civamide, and is now contending *de facto* usage of the name. One only has to investigate the 100 web pages cited in Dr. Bernstein's letter to note that the vast majority of the hits are after 1994. It is obvious that all the web pages cited have nothing to do with Winston; however, it is Winston's use of the name civamide after the name zucapsaicin was adopted that has caused the confusion and the *de facto* usage.

3. The name "zucapsaicin" violates Specific Rule #14: "A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula..."

USAN Response

The rule continues to state, "...Subsequently, if a name is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing name:"

Capsaicin, a well known entity, exists in nature, and was originally isolated in the 1890's. The chemically synthesized form, zucapsaicin, was submitted to the USAN Council long after capsaicin was marketed. Capsaicin is therefore considered to be the new chemical entity, according to this rule, and zucapsaicin is the subsequent form. There is therefore no violation to this rule in the determination of the name zucapsaicin. As pointed out in our letter dated May 23, 2003, the substance in question is a geometric isomer. Geometric isomers are not specifically listed as examples in the rule regarding stereoisomerism because they have been presented to the USAN Council so rarely. In general, geometric isomers have been developed as single isomers. However, the rule is relevant in this case because including the existing name to a stereoisomer is necessary in order to correctly identify the compound. Stereoisomers include not only the mirror image enantiomers, but also geometric (cis/trans) isomers and diastereoisomers (isomers of drugs with more than one chiral center that are not mirror images of one another).

The USAN Council is well aware of the FDA's policy statement on stereoisomeric drugs. However, this document refers to pharmacologic and toxicologic properties, and specifications for the final product. This document makes no reference to nomenclature.

As pointed out in our letter of May 23, 2003, there would be no reason for any pharmaceutical company to investigate the properties of stereoisomers if there was no medical or economic benefit in doing so. Stereoisomers can show remarkable selectivity in biological systems, and can have different biologic actions. Presumably, this is the reason that zucapsaicin is an investigational drug. However, as was also pointed out in our earlier letter, it is important for physicians and other health practitioners to know that

zucapsaicin is an isomer of capsaicin. More confusion would be caused by giving zucapsaicin a nonproprietary name that does not reflect any relationship to its optical isomer.

Selecting a Name Without Reference to Capsaicin would be Misleading to Health-Care Practitioners

USAN Response

Zucapsaicin is a geometric isomer of capsaicin. Naming this substance without reference to capsaicin would be in conflict with the principles of the USAN Council and the INN Committee, would confer the wrong information about the product, and would be misleading to health care practitioners and to the public.

Zucapsaicin is the name that has been included in the *USP Dictionary of USAN and International Drug Names* since 1994. It is, by law, the FDA-recognized, established nonproprietary name for this entity. Regardless, Winston continued to use the name civamide in the literature and in its documentation to the FDA. If Winston contends that zucapsaicin rather than civamide is misleading, it is due to their own efforts to circumvent the use of the established nonproprietary name. Civamide gives no indication as to the nature of the compound. Zucapsaicin obviously shows the relationship to capsaicin.

The USAN Council contends that zucapsaicin is indeed consistent with General Rule #1. First of all it is useful for health practitioners, especially physicians, pharmacists, nurses, etc. to understand what compound is being given to a patient. Zucapsaicin clearly identifies this compound as an isomer of capsaicin. According to General Rule #1a, "*The primary criterion for judging usefulness is suitability, including safety for use in the routine process of prescribing, ordering...*". Civamide gives no indication that this compound is an isomer of capsaicin. Some side effects inherent in capsaicin, even in a lesser form, exist in its isomer. Any information on products containing zucapsaicin would be handled in the FDA-approved labeling, which would be released by Winston only after approval of a New Drug Application by the FDA.

General Rule #1b indicates that the second criterion is "*...suitability for educational programs for students in medically oriented professions and for use in scientific and lay publications...*". Zucapsaicin is indeed suitable for this purpose as it clearly identifies the compound in question.

General Rule #1c indicates that the third criterion is "*...suitability for use internationally for drug identification, the exchange of information,...*" Zucapasaicin was adopted as a USAN after successful negotiation not only with Winston's predecessor, but with the INN Committee. The name zucapsaicin is the recommended international nonproprietary name (rINN) for this substance, and is thus recommended for use in all WHO member countries. For example, the European Union (EU) must use the rINN for labeling

purposes. More confusion would be generated not only in the US, but world-wide if the name was changed at this point.

The Council has No Reason to Conclude that Having the Names "capsaicin" and "zucapsaicin" will result in Harm to Patients

USAN Response

1. Precedents in this area, as listed in our letter of May 23, 2003, for stereoisomers, e.g., omeprazole and esomeprazole, citalopram and escitalopram, etc., indicate that names selected for stereoisomers have not resulted in harm to patients, but in fact have been useful to health care practitioners and patients in noting that the compounds are related. There have, however, been precedents set for look-alike/sound-alike names with the same vowel sequence and syllables. Civamide clearly has the same vowel sequence as rifamide, cisapride, etc. The prefix "zu" is a strong prefix which clearly differentiates zucapsaicin from capsaicin.
2. The USAN Council has not explicitly addressed the relative costs of changing a nonproprietary designation, as the Council does not consider this to be an issue in nonproprietary nomenclature. There would be minor costs incurred if the name was to be changed at this point in time. However, if the USAN Council felt that the change was justified, as it did in the amrinone/inamrinone situation, the cost in changing the name would not be taken into consideration, as patient safety is definitely the most important factor.

The USAN Council has been and continues to be pro-active in reducing medication errors. New names are carefully screened for conflict with other existing proprietary and nonproprietary names. Objections are made to proposed trademarks that infringe on other names. The USAN Council works closely with the Medication Errors Program at the USP, with the ISMP, and reviews potential tradename candidates for Safe Medication Practice Consulting (SMPC).

3. Contrary to Winston's allegations, other names were considered for this compound, both before the adoption of zucapsaicin and after Winston initially contacted the USAN Council regarding the possibility of changing the name. Two rounds of ballots and a visit from representatives of GenDerm occurred before the name was adopted as a USAN in 1993. At the request of Winston, subsequent ballots were discussed in June 2000 and in June 2001 at meetings of the USAN Council. All information supplied by Winston was reviewed, and civamide, zucapsaicin, as well as other names were supplied on the ballots.

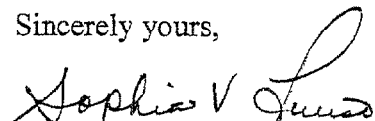
The USAN Council deliberated carefully on Winston's petitions, and came to the conclusion that this substance is an isomer of capsaicin, and, as such, the name zucapsaicin is suitable for this substance.

Conclusion

In conclusion, the USAN Council has not changed its view on this issue. After due deliberation, the USAN Council strongly believes that the name zucapsaicin is appropriate for this geometric isomer of capsaicin, and that the name was coined in accordance with its Guiding Principles. The prefix, zu-, serves to differentiate this name from capsaicin. The name zucapsaicin clearly indicates that this substance is related to capsaicin, which is appropriate. Selecting another name without reference to capsaicin would be misleading to health care practitioners. The Council is unaware of any evidence to suggest the name, zucapsaicin, will cause medication errors and harm to patients. The name civamide is inappropriate for this compound, and is in conflict with existing nonproprietary nomenclature.

The Council respectfully contends that the name zucapsaicin be retained.

Sincerely yours,


Sophia V. Fuerst
Secretary, USAN Council and
Director, USAN Program

Enclosures

cc: Winston Laboratories
USAN Council Members